

**MEMORANDUM DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION**

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FROM: Dianne Murphy, MD
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Office of the Commissioner

SUBJECT: February 15th, 2005 Pediatric Advisory Committee Meeting on the Possible Risk of Cancer from use of the Topical Immunosuppressants

TO: Members of the Pediatric Advisory Committee

On February 15th, 2005 the Pediatric Advisory Committee, supplemented with expert consultants, will meet and consider approaches to communicating about and minimizing the possible risk of cancer from use of the topical immunosuppressants (calcineurin inhibitors). This memorandum provides background information on the products, on the issues to be presented, on the questions to be discussed at the meeting, and on the additional materials provided in your briefing book.

Background:

The topical immunosuppressants are the newest class of drugs approved for the treatment of atopic dermatitis (AD). This drug class includes two products: Protopic[®] (tacrolimus) Ointment (0.03% and 0.1%) and Elidel[®] (pimecrolimus) Cream 1%. Though the exact mechanism of action in AD is unknown, both products inhibit the activity of calcineurin, the activation of T-cells, and the release of cytokines and pre-formed mediators from mast cells. Of note, Prograf[®], an oral and injectable formulation of tacrolimus, is an immunosuppressant approved for prevention of organ rejection in patients receiving allogenic liver or kidney transplants.

In December 2000, Protopic[®] (topical tacrolimus) was approved for the treatment of “short term and intermittent long term therapy in the treatment of patients with moderate to severe AD in whom the use of alternative, conventional therapies is deemed inadvisable because of potential risks, or in the treatment of patients who are not adequately responsive to or are intolerant of alternative, conventional therapies”. Both strengths (0.03% and 0.1%) were approved for this indication in adults, whereas only the lower 0.3% strength was approved for treatment of AD in children two years of age and older.

In December 2001, Elidel[®] (pimecrolimus) 1% cream was approved for “short-term and intermittent long-term therapy in the treatment of mild to moderate AD in non-immunocompromised patients two years of age and older, in whom the use of alternative,

conventional therapies is deemed inadvisable because of potential risks, or in the treatment of patients who are not adequately responsive to or intolerant of alternative, conventional therapies.”

Neither Elidel[®] nor Protopic[®] is approved or recommended for children younger than 2 years of age. Phase 3 studies of Elidel[®] cream in infants 3 to 23 months of age found a higher incidence of pyrexia (32% vs. 13% vehicle) and infections [upper respiratory tract (24% vs. 14% vehicle), nasopharyngitis (15% vs. 8%), gastroenteritis (7% vs. 3%), otitis media (4% vs. 0%) and diarrhea (8% vs. 0%)]. Safety and efficacy of Protopic[®] ointment have not been established in pediatric patients below 2 years of age; use of Protopic[®] in this age group is not recommended. Neither Elidel[®] nor Protopic[®] are contraindicated for use in children younger than 2 years.

As described in the Pediatric Drug use analysis provided in Tab 8 of your briefing book, use of Protopic[®] and Elidel[®] in the pediatric population has increased substantially since approval. During the June 2003 to May 2004 period, nearly two million prescriptions were estimated to have been dispensed to pediatric patients of all age groups nationwide (among these over one-half million are estimated to have been dispensed to children younger than 2 years). The increased use of Elidel[®] has been more dramatic than that of Protopic[®] and the increased prescribing by non-dermatologists now accounts for the majority of the use of Elidel[®].

Possible risk of carcinogenesis and concerns about long-term exposure:

At the time of approval, the long-term safety profile of both drugs in humans was unknown, though both products had pre-clinical animal carcinogenicity studies that demonstrated evidence of immune suppression mediated carcinogenicity. These findings are described in the **Carcinogenesis, Mutagenesis, Impairment of Fertility** sections of the Protopic[®] and Elidel[®] labels, which are provided in Tabs 11 and 12 of your briefing book.

For Protopic[®] (topical tacrolimus), lymphomas were noted in a mouse dermal carcinogenicity study. In addition, the median time to onset of skin tumor formation was decreased in hairless mice following chronic topical dosing with concurrent exposure to ultraviolet radiation. Of note, the Prograf[®] (oral or intravenous tacrolimus) label has a box warning about the possible development of lymphoma that may result from immunosuppression, and states in the **Carcinogenesis, Mutagenesis, Impairment of Fertility** section:

“An increased incidence of malignancy is a recognized complication of immunosuppression in recipients of organ transplants. The most common forms of neoplasm are non-Hodgkin’s lymphomas and carcinomas of the skin. As with other immunosuppressive therapies, the risk of malignancies in Prograf[®] recipients may be higher than in the normal, healthy population. Lymphoproliferative disorders associated with Epstein-Barr virus infection have been seen. It has been reported that reduction or discontinuation of immunosuppression may cause the lesions to regress.”

For Elidel[®] (pimecrolimus) there was a statistically significant increase in follicular cell adenoma of the thyroid in a 2-year rat dermal carcinogenicity study; lymphoproliferative changes (including lymphoma) in a repeat dose dermal study in mice; a statistically significant increase in lymphoma in a mouse oral carcinogenicity study; and decreased median time to skin tumor

formation in hairless mice following chronic topical dosing with concurrent exposure to ultraviolet radiation. These and additional carcinogenicity studies are summarized in Tab 10 of your briefing book and in the **Carcinogenesis, Mutagenesis, Impairment of Fertility** section of each label (Tabs 11 and 12).

Given this background, there has been concern that chronic, intermittent exposure to topical immunosuppressants over a course of time could lead to an increased incidence of Hodgkin and Non-Hodgkin lymphoma as well as melanoma and non-melanoma skin cancers.

Establishment of cancer registries:

To further evaluate these concerns, the sponsors of both products (Fujisawa Healthcare Incorporated for Protopic® and Novartis Pharmaceutical Corporation for Elidel®) were asked at time of approval to conduct long-term follow up registry studies to evaluate the risk of developing systemic cancers and skin cancers in atopic dermatitis patients who had been exposed to topical immunosuppressants on a long-term, intermittent basis. Protocols for these registries have been submitted and reviewed by FDA staff but have not yet been implemented.

October 2003 Pediatric Advisory Sub-committee to the Anti-Infective Drugs Advisory Committee meeting:

On October 30th 2003, the Pediatrics Subcommittee of the Anti-Infective Drugs Advisory Committee met and discussed research design issues for the cancer registries for Elidel® and Protopic®. Many concerns about the complexities of development of these studies were discussed at this meeting, including but not limited to: the approach to defining and measuring drug exposure; the method for following up exposed children for skin and other cancers; and the need for very large registries and lengthy follow-up (10 years or more) to evaluate this potential risk because of the rarity of skin and other cancers in children and adolescents and the long latency time between exposure to a carcinogen and tumor development .

At the time of this meeting, only five malignancy related events had been reported to the FDA for Protopic® and two events had been reported for Elidel®. The committee expressed concern about these events and about off-label prescribing of Protopic® and Elidel® for children younger than 2 years. The Committee members also discussed approaches to risk management with some recommending: stronger warnings and other labeling changes, an updated patient package insert, education programs emphasizing that Protopic® and Elidel® are indicated as second-line therapy in patients older than 2 years of age, unit of use packaging that would reinforce the short-term use of these agents, and other suggestions. The content of this meeting will be summarized for you on February 15th, 2005.

Recent concerns:

The Agency has received a report of a non-human primate (monkey) study of three oral doses of Elidel where viral associated lymphomas occurred in a dose-response manner and no NO Adverse Effect Level (NOAEL) was defined. This study is described in Tab 10 of the briefing book and will be reviewed at this meeting. In addition, since the October 2003 meeting, the FDA

has received additional malignancy and other adverse reports for Elidel[®] and Protopic[®]; these are described in the recent adverse event reviews for both products in Tabs 6 and 7 of your briefing book.

The full spectrum of carcinogenic potential in animals or humans from exposure to these agents has yet to be defined. For example, systemic absorption from the topical application of Elidel[®] and Protopic[®] may occur in both adults and children. The highest level of either product was observed in a child who had extensive use on a “severe skin condition.” Whether systemic or regional absorption in the local draining lymph nodes occurs and increases regional cancer risk is technically difficult to study and has yet to be evaluated.

These recent events indicate the need for a full review of current labeling and other risk minimization efforts and consideration of what additional efforts are recommended.

The Agency has determined that there is a need for a stronger approach to the communication about and minimization of the potential risk of cancer from use of Elidel[®] and Protopic[®]. At the February 15th 2005 meeting, the Agency will provide updated background information to you on these products, including a summary of recent concerns and usage trends, pharmacologic data, animal carcinogenicity data, and adverse event reports. Many of these talks will be developed from the provided briefing materials. Jeffrey I. Cohen, MD will provide a review of Epstein-Barr virus infections and their association with subsequent cancer. You will hear an update on the Agency approach to risk minimization, including a summary of the toolbox for drug exposure risk minimization. Finally, we will ask you to advise the Agency on a series of risk management issues, which will be framed in a series of questions.

The contents of your briefing book are listed below. We have tried to limit the material provided to the most essential information you might want to review ahead of time. If your preparation time before the meeting is limited, I suggest that you focus first on the review of animal carcinogenicity data under Tab 10 (especially the new non-human primate findings which have not been presented in the past) and then on: the consultation summary provided by the Division of Pediatric Drug Development, Center for Drug Evaluation and Research (CDER), FDA; the drug usage consultation (Tab 8) and summaries of adverse events for both products from the Office of Drug Safety, CDER, FDA (Tabs 6, 7, and 9), and both product labels (Tabs 11 and 12). Two background reference articles are provided in Tabs 13 and 14.

- Tab 1 Meeting Roster
- Tab 2 Meeting Agenda
- Tab 3 Meeting Memorandum and Draft Questions
- Tab 4 January 2005 Consultation from the Division of Pediatric Drug Development, CDER, FDA
- Tab 5 Topical Immunosuppressant Slides from the Division of Dermatologic and Dental Drug Products
- Tab 6 Protopic[®] Safety Review from the Office of Drug Safety, CDER, FDA
- Tab 7 Elidel[®] Safety Review from the Office of Drug Safety, CDER, FDA
- Tab 8 Protopic[®] and Elidel[®] Use Review from the Office of Drug Safety, CDER, FDA
- Tab 9 Malignancy-Related Adverse Events from the Office of Drug Safety, CDER, FDA

- Tab 10 Pharmacology-Toxicology Review and Slides from the Division of Dermatologic and Dental Drug Products, CDER, FDA
- Tab 11 Elidel[®] (pimecrolimus) Label
- Tab 12 Protopic[®] (tacrolimus) Label
- Tab 13 Cohen JI. Epstein-Barr Virus Infection. N Engl J Med 2000; 343:481-92.
- Tab 14 Euward S, Kanitakis J, Claudy A. Skin Cancers after Organ Transplantation. N Engl J Med 2003; 348:1681-1691.

Themes to be addressed in the questions and during the Committee discussion are:

- The risk messages to be communicated;
- The need for stronger warnings and clearer information in labeling;
- How to communicate the possible cancer risk to prescribers and the public;
- Whether additional risk minimization approaches are needed; and
- How to define and measure success or failure with a risk minimization plan.

The FDA relies on external experts such as you to advise it on complex matters of science, medicine, clinical practice, and ethics as they relate to drug development. We thank you for your time, effort and thoughtful advice, and look forward to seeing you and hearing from you on February 15th 2005.